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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
ROARK, JESSICA H

ART UNIT	PAPER NUMBER
1644	

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19

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/646,561	Applicant(s) SIM ET AL.	
	Examiner Jessica H. Roark	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,6,8,10-14,16-19,21,23,25-27 and 37-39* is/are pending in the application.

4a) Of the above claim(s) *39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6,8,10-14,16-19,21,23,25-27,37 and 38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *12* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. *Claims* 1-3, 6, 8, 10-14, 16-19, 21, 23, 25-27 and 37-39 *are pending.*

2. Applicant's election of a species that is canine B7-2 in Paper No. 18 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

However, because the full length nucleic acids encoding canine B7-2 appear to be free of the art, the sequences drawn to feline B7-2 have been rejoined and fully examined for patentability.

Claim 39 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 16.

Claims 1-3, 6, 8, 10-14, 16-19, 21, 23, 25-27 and 37-38 *are under consideration in the instant application.*

Priority

3. Applicant's claims for domestic priority under 35 U.S.C. 119(e) and 35 U.S.C. 120 are acknowledged.

The following assessment of priority has been made by the Examiner based upon provisional application 60/078,765 (filed 03/19/1998) and U.S.S.N. 09/062,597 (filed 04/17/1998):

instant claims	'597	'765
canine B7-2 of SEQ ID NOS:6, 8-10	yes	yes
soluble canine B7-2 of SEQ ID NOS:16, 18-20	yes	yes
feline B7-2 of SEQ ID NOS: 25, 27-29	yes	no
PCR clone 1 of SEQ ID NOS:30 and 32	no	no
PCR clone 2 of SEQ ID NOS:33 and 35 (partial soluble)	no	no
canine B7-2 function of T cell proliferation	yes	no
feline B7-2 function of CTLA4 binding	no	no

A claim as a whole has only one effective filing date. See e.g. Studiengelsellschaft Kahle m.b.H. v. Shell Oil Co. 42 USPQ2d 1674, 1677 (Fed. Cir 1997).

Thus provisional application 60/078,765 (filed 03/19/1998) fails to provide adequate support under 35 U.S.C. 112 for claims 1-3, 6, 8, 10-14, 16-19, 21, 23, 25-27 and 37-38 of this application.

Similarly, U.S.S.N. 09/062,597 (filed 04/17/1998) fails to provide adequate support under 35 U.S.C. 112 for claims 1-3, 6, 8, 10-14, 16-19, 21, 23, 25-27 and 37-38 of this application.

Claim 3 is included because although the words are present in the applications to which domestic priority is claims, for the reasons set forth below in the rejection under 35 USC 112, first paragraph, written description, this claim language fails to meet the written description requirement.

Thus the effective filing date of the instant claims is considered to be the filing date of the instant application, i.e., 3/19/1999.

Should Applicant disagree with the Examiner's factual determination above, *it is incumbent upon the Applicant to provide a showing that specifically supports the instant claim limitations.*

IDS

4. Applicant's IDS, filed 6/24/02 (Paper No. 12), is acknowledged.

Reference A2 was not found as part of the instant file and thus has not been considered at this time. Applicant is invited to provide another copy of this reference so that it may be considered and the instant file completed. The Examiner apologizes for the inconvenience to Applicant.

Specification

5. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which Applicant may become aware in the specification.

Claim Rejections - 35 USC § 112 second paragraph

6. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 12, 17-19 and 38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claim 12 is indefinite in the recitation of designators such as "nCaB7-2_{1897}" because their characteristics are ambiguous and unclear. It is not clear whether these lab designations refer to discrete B7-2 nucleic acid sequences, or if they refer to plasmids comprising B7-2 encoding nucleic acids. The use of these laboratory designations as the sole means of identifying the claimed sequence/plasmids renders the claim indefinite because these are merely laboratory designations which do not clearly define the claimed products, since different laboratories may use the same laboratory designations to define completely distinct biological materials.

Applicant may obviate this rejection by providing depository accession number in the claims, provided these are plasmids, or alternatively, if these are discrete sequences or subsequences, then the provision of the appropriate SEQ ID NO: and other identifying information may obviate this rejection.

B) Claims 17-19 recite a recombinant molecule, recombinant virus, or recombinant cell comprising a nucleic acid molecule as set forth in claim 8. However, claim 8 recites a method to produce a protein. Therefore there is a lack of antecedent basis for claims 17-19 as currently recite. It is suggested that Applicant delete the reference to claim 8 in claims 17-19.

C) Claim 38 recites "said therapeutic compound". However, claim 6 from which claim 38 depends recites a therapeutic composition and there is therefore a lack of antecedent basis for "said therapeutic compound" It is suggested that Applicant amend claim 38 to recite -- said therapeutic composition --.

D) Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

Claim Rejections - 35 USC § 112 first paragraph

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-3, 6, 8, 10-11, 13-14, 16-19, 21, 23, 25-27 and 37-38 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The following *written description* rejection is set forth herein.

The claims recite:

A) "% identity" language including "at least about 80% identical" to a nucleic acid sequence and "at least about 60% identical" to an amino acid sequence;

B) "fragments comprising" language including "fragments" of nucleic acids having at least about 12 or at least about 18 nucleotides and a nucleic acid molecule that comprises an oligonucleotide;

C) "allelic variants" of nucleic acids; and

D) a genus of nucleic acids encoding "naturally-occurring soluble mammalian" B7-2 proteins.

The Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 3rd column).

Regarding the instant claim limitations, the specification does not appear to provide an adequate written description for the following reasons:

A) "Percent Identity":

The claims recite a genus of nucleic acid molecules which differ in sequence to varying extents from the nucleic acids of SEQ ID NOS: 6, 9, 16, 19, 25, 28, 30 and 33 (the full length complements of which are set forth in SEQ ID NOS:8, 10, 18, 20, 27, 29, 32 and 35, respectively). The claims do not require that the instant nucleic acids share any testable functional activity of the polypeptides encoded by the instant nucleic acids, a feature deemed essential to the instant invention. Applicant has disclosed only canine and feline B7-2, and a soluble variant of each and thus has disclosed only a limited number of species. However, the instant claims are drawn to an extensive genus of nucleic acids. In the absence of a particular testable function and some structural basis for that function that must be maintained by the members of the genus, the claimed invention is not described in such a way as to reasonably convey to one of ordinary skill in the art that the inventor, at the time the application was filed, had possession of the invention. See Regents of the University of California v. Eli Lilly & Co., 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). Applicant is also directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

B) "Fragments Comprising":

Fragment language that encompasses either percent identity language, or open claim language (comprising/having) which thereby permits unidentified flanking sequence to be added, does not allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. Fragments which comprise unidentified flanking sequence or have variation within their sequence thus do not meet the written description requirement. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (id at 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (id at 1116.).

C) "Allelic Variants":

The term "allelic variants" encompasses any gene that occurs at essentially the same locus in the genome as the reference gene, as disclosed in the specification as-filed on page 14, lines 1-5. However, there is insufficient written description in the specification of such allelic variants of B7-2. First it is noted that there is no written description of genomic DNA in the specification: the instant SEQ ID NOS are derived from cDNA libraries. cDNA does not provide an adequate written description of genes and allelic variants thereof because no information is provided as to whether the genomic DNA has introns, where said introns are located, etc. In addition, allelic variants do not necessarily encode proteins having the same function. For example, Voet et al. (In Biochemistry. John Wiley & Sons. 1990, Vol.1, pages 126-128, and page 230) teaches that allelic variation in the β subunit of hemoglobin results in drastically different functions, even though the proteins share a high level of sequence and structural homology.

The Federal Circuit has held that if an inventor is "unable to envision the detailed constitution of a gene so as to distinguish it from other materials. . .conception has not been achieved until reduction to practice has occurred", Amgen, Inc. v. Chugai Pharmaceutical Co, Ltd., 18 USPQ2d 1016 (Fed. Cir. 1991). Thus the term "allelic variant" fails to provide a structure for which a function can be correlated, and in the absence of additional support in the specification as filed, the term "allelic variant" does not meet the written description provision of 35 U.S.C. 112, first paragraph.

D) Nucleic acids encoding "naturally-occurring soluble mammalian" B7-2 proteins:

The specification discloses that a nucleic acid encoding a "naturally-occurring soluble mammalian" B7-2 protein may be isolated from *any* mammalian species (page 20 at lines 17-24). Thus the genus recited is very large. As noted supra the specification discloses SEQ ID NOS:16 (full length) and 19 (coding), nucleic acids encoding a naturally-occurring soluble canine B7-2 protein; and SEQ ID NO: 33, a partial sequence for a nucleic acid encoding a naturally-occurring soluble feline B7-2 protein. Thus the specification provides at most two members of the instant genus of any nucleic acid encoding a "naturally-occurring soluble mammalian" B7-2 protein.

However, in University of California v. Eli Lilly and Co., 39 USPQ2d 1225 (Fed. Cir. 1995); the inventors claimed a genus of DNA species encoding insulin in different vertebrates or mammals, but had only described a single species of cDNA which encoded rat insulin. The Court held that only the nucleic acids species described in the specification (i.e. nucleic acids encoding rat insulin) met the description requirement and that the inventors were not entitled to a claim encompassing a genus of nucleic acids encoding insulin from other vertebrates, mammals or humans, id. at 1240. Therefore, the specification does not provide sufficient written support for the genus of nucleic acids encoding any "naturally-occurring soluble mammalian" B7-2 protein, irrespective of the inclusion of functional limitations. A description of what a material does, rather than of what it is, usually does not suffice. Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406.

Therefore, the specification fails to provide an adequate written description of the above noted claim limitations.

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Alternatively, Applicant is invited to point to clear support or specific examples of the claimed invention in the specification as-filed.

10. Claims 1-3, 6, 8, 10-11, 13-14, 16-19, 21, 23, 25-27 and 37-38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for isolated nucleic acids comprising SEQ ID NOS:6, 8-10, 16, 18-20, 25, 27-30, 32-33 and 35 and nucleic acids encoding proteins comprising SEQ ID NOS:7, 17, 26 and 34; does not reasonably provide enablement for

A) nucleic acids "at least about 80% identical" to another nucleic acid sequence and nucleic acids encoding amino acid sequences "at least about 60% identical" to an amino acid sequence ("% identity language");

B) "fragments comprising", including "fragments" of nucleic acids having at least about 12 or at least about 18 nucleotides and a nucleic acid molecule that comprises an oligonucleotide;

C) "allelic variants" of nucleic acids; and

D) nucleic acids encoding "naturally-occurring soluble mammalian" B7-2 proteins.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The specification discloses nucleic acids encoding canine and feline B7-2, either as nucleic acids including 5' and 3' untranslated regions (SEQ ID NO:6, canine; SEQ ID NO:25, feline), or as limited to coding regions (SEQ ID NO:9, canine; SEQ ID NO:28, feline), and the full length complements of each of these nucleic acids (SEQ ID NOS:8 and 10, canine; SEQ ID NOS:27 and 29, feline). The specification also discloses cDNA encoding a full length canine soluble B7-2 protein in which the transmembrane domain has been deleted (SEQ ID NOS: 16 and 19 (coding region)), and the full length complements of said nucleic acids (SEQ ID NOS: 18 and 20). A PCR clone containing a cDNA of a partial feline soluble B7-2 is also disclosed (SEQ ID NO: 33) and the full length complements of said nucleic acids (SEQ ID NO:35). Finally, the specification discloses a PCR clone of a feline cDNA corresponding to a portion of the full length sequence (SEQ ID NO:30 and SEQ ID NO:32, full length complement).

The specification discloses that the canine B7-2 protein when transfected in CHO cells will stimulate resting T cells (i.e., functions to costimulate T cell proliferation, Example 4 pages 59-60). The specification also discloses that the feline B7-2 protein expressed in L cells will bind CTLA4 (e.g., Examples 8 and 9, pages 66-68).

A) "Percent Identity":

The state of the art at the time the invention was made recognized that even single amino acid differences can result in drastically altered functions between two proteins. For example, Metzler et al. (Nature Structural Biol. 1997; 4:527-531) showed that any of a variety of single amino acid changes can alter or abolish the ability of CTLA4 to interact with its ligands CD80 and CD86 (B7-1 and B7-2) (e.g., summarized in Table 2). The variation in function among "B7-like" polypeptides is further emphasized by the teachings of Coyle et al. (Nature Immunol. 2:203-209 2001) who show that the B7-like family members have distinct expression patterns *and distinct functions* (see in particular Figures 2 and 3). Given the extensive variation permitted by recitations such as "at least about 60% identical" for the encoded polypeptide sequence, the skilled artisan would not reasonably expect such variant proteins to have the same function as the instantly recited SEQ ID NOS, particularly when the family of B7-like proteins was known to have variable function.

Finally, although some of the claims require that the nucleic acid encode a variant protein that retains an antibody epitope, this limitation fails to provide sufficient guidance with respect to the protein containing the epitope. An antibody epitope may be as small as 6-15 shared amino acid residues (e.g., Lerner Nature 1982; 299:592-596, see page 595-596) and places no limitations on the function of the protein containing the polypeptide sequence recognized by the antibody.

Therefore, it is unpredictable if any functional activity will be shared by two polypeptides having less than 100% identity over the full length of their sequences. The specification does not appear to provide sufficient guidance as to which nucleic acid residues should or should not be changed to preserve any particular function. Although the specification does provide working examples of nucleic acids encoding canine and feline B7-2, including a soluble form thereof, the variation permitted by the instant percent identity language is extensive. Consequently, the experimentation left to those skilled in the art to determine which nucleic acids having "at least about 80%" identity or nucleic acids encoding proteins "at least about 60% identical" would encode proteins having the same function as those recited is unnecessarily, and improperly, extensive and undue.

Even in view of the functional limitations included in some of the claims, the skilled artisan still lacks sufficient guidance with respect to which changes can be made while maintaining the recited function. Such guidance requires knowledge as to which encoded amino acids actually contribute to the recited function versus which encoded amino acids are non-essential to the function. The instant specification does not appear to provide this knowledge and guidance with respect to an assignment of function to specific amino acids. Thus the recitation of percent identity language permitting extensive sequence variation, whether with respect to the polypeptide or nucleic acid encoding the polypeptide, and particularly in the absence of *a testable function* and limitations regarding the *sequence length over which the percent identity is required*; does not allow the skilled artisan to make and use the encoding nucleic acids commensurate in scope with the instant claims without undue experimentation.

It is suggested that Applicant limit the claims to variant nucleic acids sequences having only limited variation (e.g. 95% identity) *over the full length* of the sequence, and *possessing testable functional activity* (e.g. stimulation of T cell proliferation and/or binding to CTLA-4).

B) "Fragments Comprising":

The instant claims recite in various forms "fragments having" a certain number of nucleotides of the various SEQ ID NOS. "Having" is considered "open" claims language, equivalent to "comprising", and opening the claim up to the inclusion of additional nucleotides of undisclosed identity and number flanking the recited "fragment having". The skilled artisan can make fragments *limited* to subsequences of the individual SEQ ID NOS and use them (e.g., as nucleic acid probes or PCR primers) without undue experimentation. However, before the skilled artisan can make "fragments having" additional flanking sequence, guidance is required with respect to the identity of those flanking sequences. In the instant case however, the specification does not appear to provided this needed guidance. Further, although some of the claims require that the nucleic acid fragments encode an antibody epitope, this limitation in not a functional limitation since an antibody epitope may be as small as 6-15 shared amino acid residues (e.g., Lerner Nature 1982; 299:592-596, see page 595-596) and places no limitations on the function of the protein containing the polypeptide sequence recognized. Therefore the scope of the instant claims encompassing "fragments comprising" does not appear to be commensurate with the enablement provided by the instant disclosure.

C) "Allelic Variants":

The term "allelic variants" encompasses any gene that occurs at essentially the same locus in the genome as the reference gene, as disclosed in the specification as-filed on page 14, lines 1-5. As noted supra, the specification does not appear to provide an adequate written description of "allelic variants" of the instant sequences; thus the specification fails to provide sufficient guidance as to how to make allelic variant sequences. In addition, allelic variants do not necessarily encode proteins having the same function. For example, Voet et al. (In Biochemistry. John Wiley & Sons. 1990, Vol.1, pages 126-128, and page 230) teaches that allelic variation in the β subunit of hemoglobin results in drastically different functions, even though the proteins share a high level of sequence and structural homology. Thus even had the specification clearly taught how to make allelic variants of the instant sequences, the skilled artisan still would not know how to use them. Consequently, the scope of claims reciting "allelic variants" does not appear to be commensurate with guidance provided in the specification as filed, and it would require undue experimentation of the skilled artisan to make and use such nucleic acid sequences.

D) Nucleic acids encoding "naturally-occurring soluble mammalian" B7-2 proteins:

The specification discloses that a nucleic acid encoding a "naturally-occurring soluble mammalian" B7-2 protein may be isolated from *any* mammalian species (page 20 at lines 17-24). Thus the scope of the instant claims is extensive. The specification discloses SEQ ID NOS:16 (full length) and 19 (coding), nucleic acids encoding a naturally-occurring soluble canine B7-2 protein; and SEQ ID NO: 33, a partial sequence for a nucleic acid encoding a naturally-occurring soluble feline B7-2 protein. Thus the specification provides at most two members of the instant genus of any nucleic acid encoding a "naturally-occurring soluble mammalian" B7-2 protein.

However, there is insufficient biochemical or structural information to enable the skilled artisan to make and use any nucleic acid encoding a "naturally-occurring soluble mammalian" B7-2 protein, as broadly claimed. The breadth of the instant claim is extensive, encompassing any nucleic acid that encodes a B7-2 protein that is soluble for *any* reason (e.g., lacking a transmembrane domain only, lacking all sequence at the carboxy terminus, lacking all domains except the IgV domain, etc.) and that is found in *any* mammalian species. The instant claims are essentially a wish to know the identity of any nucleic acid meeting these general parameters. It has been previously decided that claims recitations so broad do not provide sufficient guidance as to how to make and use the claimed invention. See Colbert v. Lofdahl, 21 USPQ2d, 1068, 1071 (BPAI 1992).

Thus with respect to these claim limitations, each of which encompass considerable breadth and for each of which the specification provides only limited guidance; it would require undue experimentation of the skilled artisan to make and use such nucleic acid sequences; thus the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

11. Claims 6, 10-14, 16-19, 26-27 and 37-38 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims recite a "therapeutic composition" comprising a nucleic acid encoding a canine or feline B7-2 protein, that, when administered to an animal, regulates T cell mediated immune responses in said animal.

As noted supra, the specification does not appear to provide sufficient guidance with respect to percent identity language and allelic variants such that the skilled artisan could practice the invention without undue experimentation. However, even were the instant claims limited to nucleic acid sequences for which the specification is enabling, the specification still would not provide sufficient guidance such that the skilled artisan could make use these nucleic acids as therapeutic compositions without extensive additional experimentation.

The use of therapeutic compositions comprising inhibitory (antisense) or stimulatory (sense) DNA, as disclosed in the specification at pages 43-51 was well known in the art to be highly unpredictable, even though the level of skill in the art is high. For instance, Mountain reviews in TIBTECH (18:119-128 2000) that while much progress has been made in the field of gene therapy, developing effective gene therapies is much more demanding than originally anticipated (e.g., pg 120, middle); and that most of the difficulty lies with the development of effective vectors since the vectors in use all have both advantages and disadvantages (e.g., Table 4). Mountain concludes that it is unlikely that a universal vector will emerge in the next few years (page 125, middle of 1st column). Similarly, although antisense therapy has progressed in recent years, there is still a high level of unpredictability in the art. This unpredictability was summarized recently by Branch (TIBS 1998; 23:45-50). In particular, difficulties in ensuring that the oligo interacts with its single gene target versus other genes, and a variety of unexpected non-antisense effects, complicate the use of antisense compounds (e.g., summarized in Abstract). Thus in the absence of working examples or detailed guidance in the specification, the intended uses of any therapeutic composition comprising a nucleic acid is fraught with uncertainties.

Therefore, given the uncertainties associated with *in vivo* therapies employing nucleic acids and in view of the lack of guidance provided in the specification; it would require undue experimentation for the skilled artisan to utilize a therapeutic composition comprising the instant nucleic acids encoding canine or feline B7-2 proteins.

12. Claims 8, 14 and 26 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make use the invention.

Claim 8 recites a method to produce a B7 protein. However, SEQ ID NOS:8, 10, 18, 20, 27, 29, 32 and 35 are not coding sequences, they are the complementary sequences. The specification discloses uses for B7 protein, not for protein produced by expressing these complementary sequences. Therefore, it would require undue experimentation of the skilled artisan to use the complementary nucleic acid sequences to express a B7 protein.

It is suggested that Applicant delete SEQ ID NOS which are complementary sequences from any claim requiring expression of the protein.

13. Claim 12 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In claim 12 it is apparent that the nCaB7-2_{1897}, nCaB7-2_{987}, nCaB7-$2s_{1795}$, nCaB7-2_{840}, nFeB7-2_{2830}, nFeB7-2_{996}, nCaB7-2_{921}, nCaB7-$2s_{774}$, nFeB7-2_{918} nFeB7-2_{509} and nFeB7-2_{359} plasmids are required to practice the claimed invention. As required elements, they must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If not so obtainable or available, the enablement requirements of 35 USC 112, first paragraph, may be satisfied by a deposit of these plasmids. See 37 CFR 1.801-1.809.

In addition to the conditions under the Budapest Treaty, Applicant is required to satisfy that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, Applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If the original deposit is made after the effective filing date of an application for patent, the applicant should promptly submit a verified statement from a person in a position to corroborate the fact, and should state, that the biological material which is deposited is a biological material specifically identified in the application as filed, except if the person is an attorney or agent registered to practice before the Office, in which the case the statement need not be verified. See MPEP 1.804(b).

35 U.S.C. §§ 102 and 103

14. The following rejections under 35 U.S.C. §§ 102 and 103 are made under the assumption that the effective filing date of the instant claims is the filing date of the instant application, i.e., 3/19/1999.

It is noted that claims *limited to canine B7-2 sequences* would appear to be entitled to an earlier effective filing date that would obviate certain rejections set forth below.

Claim Rejections – 35 U.S.C. §§ 102 and 103

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

16. Claims 1-3, 6, 8, 10-11, 13-14, 16-17, 19, 23, 25, 27 and 37 are rejected under 35 U.S.C. 102(b) as being anticipated by Maher et al. (J. Immunol. 157: 3838-3844, 1996; 1449).

Maher et al. teach nucleic acids encoding a porcine B7-2 proteins, recombinant molecules and recombinant cells comprising the nucleic acid, and methods of producing the B7-2 protein (see entire document, especially Figure 2 and Materials and Methods). The porcine B7-2 nucleic acid of Maher et al. has greater than 80% nucleic acid sequence identity, at least over partial sequence lengths, when compared to the instant SEQ ID NOS, and is encompassed by the instant claimed nucleic acid molecules, particularly with respect to "60/80 sequence identity", "allelic variant", "having or comprising a fragment/oligonucleotide", "therapeutic compositions comprising", etc. Maher et al. also teach transfected cells, which meet the limitation of a carrier.

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations of CD28/CTLA4 binding, T cell costimulation, regulating/eliciting an immune response, etc. would be inherent properties of the referenced B7-2 encoding nucleic acid molecules, vector and host cells expressing said nucleic acid as well as their use to express B7-2 protein. It is noted that given that the only active ingredient in the composition is the nucleic acid, then the prior art reads on claims 6 and 37. In addition, although the nucleic acid of Maher et al. encodes a transmembrane domain, the isolated protein would nevertheless be soluble and thus meets the limitations of instant claim 3.

17. Claims 1-3, 6, 8, 10-11, 13-14, 16-19, 21, 23, 25-27 and 37-38 are rejected under 35 U.S.C. 102(e) as being anticipated by Collisson et al. (US 2002/0028208 A1, see entire document).

Collisson et al. teach the nucleic acid of SEQ ID NO:5 (see e.g., sequence listing). SEQ ID NO:5 is a nucleic acid encoding a feline B7-2 protein (see entire document, e.g., paragraph 28 and Figure 3A).

SEQ ID NO:5 of Collisson et al. is an isolated nucleic acid which is a coding region that is 87% identical to the coding region set forth in SEQ ID NO:9, and is therefore also 87% identical to the coding region (residues 6-992) of SEQ ID NO:6.

SEQ ID NO:5 of Collisson et al. is an isolated nucleic acid which is a coding region that is 82% identical to the coding region set forth in SEQ ID NO:19, and is therefore also 82% identical to the coding region (residues 7-846) of SEQ ID NO:16.

SEQ ID NO:5 of Collisson et al. is an isolated nucleic acid which is a coding region that is 98% identical to the coding region set forth in SEQ ID NO:28, and is therefore also 98% identical to the coding region (residues 179-1174) of SEQ ID NO:25.

Nucleotides spanning approximately positions 547 to 1010 of SEQ ID NO:5 of Collisson et al. are also 100% identical to SEQ ID NO:30 from 1-466; and nucleotides spanning approximately positions 547 to 1056 of SEQ ID NO:5 are 98% identical to SEQ ID NO:30 from 1-509.

Nucleotides spanning approximately positions 547 to 772 of SEQ ID NO:5 of Collisson et al. are also 100% identical to SEQ ID NO:33 from 1-227; and nucleotides spanning approximately positions 547 to 907 of SEQ ID NO:5 are 79% identical to SEQ ID NO:33 from 1-359.

SEQ ID NO:5 of Collisson et al. includes numerous fragments of the SEQ ID NOS set forth above having at least 12 or at least 18 nucleotides, and these fragments would inherently encode an epitope.

The complement of SEQ ID NO:5 is also taught (e.g., paragraph 70), which therefore anticipates the instant complementary sequences set forth in SEQ ID NOS:8, 10, 18, 20, 27, 29, 32 and 35 for the reasons set forth supra.

Further, given the identity shared by SEQ ID NO:5 of Collisson et al. and the instant nucleic acids, SEQ ID NO:5 therefore inherently encodes a protein having at least about 60% identity to the proteins encoded by the nucleic acid sequences set forth above, i.e., the proteins of instant SEQ ID NOS:7, 17 and 26, or at least 80% identical to the protein of instant SEQ ID NO: 34, *particularly since there is no requirement that the percent identity be over the full length of the sequence.* The encoded B7-2 protein would also inherently elicit an immune response against a naturally-occurring B7-2 protein since SEQ ID NO:5 itself encodes a naturally-occurring B7 protein.

The isolated nucleic acid of Collisson et al. set forth in SEQ ID NO:5 can also broadly be considered an allelic variant of at least SEQ ID NOS: 25 and 28, since each encode a feline B7-2 protein but differ from each other by a few nucleotide residues.

Collisson et al. also teach formulation of the nucleic acid of SEQ ID NO:5 in therapeutic compositions to regulate T cell immune responses (e.g., paragraphs 59, 94 and 103-106). Formulations including excipients, adjuvants and carriers are also taught (e.g., paragraph 106), as are both naked nucleic acid vaccines and a recombinant cell vaccine (e.g., paragraphs 73, 94 and 103-104).

Collisson et al. also teach linking the nucleic acid of SEQ ID NO:5 to transcription control sequences, and recombinant cells and viruses comprising said nucleic acid and methods of producing a B7-2 protein (e.g., paragraphs 70-74).

Finally, Collisson et al. teach nucleic acids encoding soluble feline CD86 lacking the transmembrane domain (e.g., paragraphs 44 and 55). It is noted that the B7-2 protein encoded by the nucleic acids of Collisson et al. would inherently be soluble, bind either or both of CD28 and CTLA4 and would deliver a co-stimulatory signal to a helper T cell sufficient to stimulate cytokine secretion (see also paragraphs 54-55).

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the nucleic acid of SEQ ID NO:5.

The reference teachings thus anticipate the instant claimed invention.

Conclusion

18. No claim is allowed.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jessica Roark, whose telephone number is (703) 605-1209. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

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December 27, 2002

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